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Antimicrobial Drug Consumption on Swiss Pig Farms: A Comparison of Swiss and European Defined Daily and Course Doses in the Field

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Keywords: antimicrobial drug usage, antimicrobial classes, defined daily dose, defined course dose, European medicines agency, monitoring systems, pigs, Switzerland

INTRODUCTION

Antimicrobial use (AMU) is associated with the selection of resistant pathogens (1, 2) and the spread of resistance both within and between human and veterinary medicine (3–5). Responsible use of antimicrobials is therefore essential (6).

The importance of antimicrobial resistance for public health is internationally acknowledged (7, 8) and AMU in food-producing animals is monitored by various authorities (9, 10) in order to determine trends in resistance development.

In addition to monitoring systems measuring the amount of active ingredients, systems based on application equivalents have been established in several countries to monitor AMU in veterinary medicine (11–13). These application equivalents, originally developed for humans (14), standardize the measurement of AMU (15), by taking into account the dosages of the various antimicrobial compounds, and defining a dosage required daily or for a whole treatment. In line with the formal definition of the World Health Organization (WHO), Defined Daily Doses (DDD) and Defined Course Doses (DCD) are the assumed average maintenance doses per day or total treatment duration (16), which allow the estimation of number of treatment days respectively, number of treatments in a population (17).

In 2016, following these principles, the European Medicines Agency (EMA) published average defined daily dose (DDDvet) and defined course dose (DCDvet) values for antimicrobial agents used in livestock production as a tool to facilitate standardized collection and presentation of AMU among European member states (18). These values were defined by calculating the mean of given registrations for livestock production from nine different European countries. In analogy with the principles of the EMA (19), national defined doses (DDDch and DCDch) for each individual registration in the pig sector in Switzerland were recently determined and some theoretically discrepancies between Swiss and European values have been described in a prior study (20).

The aim of this study was to investigate the outcome of calculated antimicrobial consumption in the field based on either individual, Swiss values (DDDch/DCDch) or average, European values (DDDvet/DCDvet). The impact of using either DDD/DCDch or DDD/DCDvet values were tested for different age groups, administration routes and antimicrobial classes. Moreover, the impact of using either DDD/DCDch or DDD/DCDvet for evaluation of antimicrobial use on the study

classes can the most frequent AMU be observed in the pig sector of Switzerland?

MATERIALS AND METHODS

Data Collection

In cooperation with the Swiss Swine Health Service (SSHS), data from 227 Swiss pig farms concerning antimicrobial use in 2015 was collected, thus representing 3.3% of all pig farms in Switzerland in 2015 (21). All 227 farms joined a nationwide voluntary program for pig producers in Switzerland in order to evaluate and improve transparency of AMU on their farms. Only farms with a complete documentation of antimicrobial ingredients purchased in the year 2015 were included in the study. The study farms were required to provide documentation of all veterinary prescriptions of antimicrobials for this year, including exact information about the name and the amount of the used products. Farmers were required to allocate the prescribed antimicrobials to four different groups (sow, finisher pig, weaner, and piglet). The documentation had to be reported once every 3 months during the year. In addition to AMU records, numbers of pigs kept (sows) or produced annually (all other age groups) and the type of farm were also documented. Overall 96 piglet-producing farms, 42 farrow-to-finish pig farms and 89 finishing farms housing a total of 328,909 piglets, 292,298 weaners, 179,144 finishing pigs and 11,710 sows were included in the study. The number of sows were representing 9.5% of all sows kept in Switzerland, which were notified in 2015 (21). The mean farm size was 85 sows with 2,383 produced piglets and 2,108 produced weaners in the year 2015, including the data of all piglet-producing and farrow-to-finish farms. The mean of the produced finishing pigs was 1,303, combined the data of the farrow-finish farms and the finishing farm, respectively. A piglet-producing farm housing at least 30% piglets from birth until time of slaughter was considered as farrow-to-finish farm.

AMU Quantification

In order to quantify AMU, the amount of prescribed antimicrobial ingredient during the year 2015 of all participating farms was divided by the defined doses (DDD/DCDvet or DDD/DCDch) of the corresponding antimicrobial classes multiplied by the standard weights of the different age groups as defined by the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) (piglets: 4 kg; weaners: 12 kg; finisher pig: 50 kg and sow: 220 kg) (22).

$$\text{Number of Defined Doses} = \frac{\text{total amount of prescribed antimicrobial ingredient (mg)}}{\text{DDDvet or DDDch or DCDvet or DCDch} \left(\frac{\text{mg}}{\text{kg}} \right) \times \text{standard weight of age group (kg)}}$$

farms was considered, as well as differences in antimicrobial usage by farm type.

The questions behind all these investigations were: Will an AMU monitoring system based on either Swiss or European definitions lead to comparable results in the field or not? And for which age groups, administration routes and antimicrobial

The recently published, national defined daily and course doses for the pig sector in Switzerland were drawn up in accordance with the principles of the EMA (19). In order to establish DDDch and DCDch, the required information on dosage and treatment duration was generally taken from the product approvals which are summarized in the

TABLE 1 | Total and relative antimicrobial use (AMU) on 227 Swiss pig farms in the year 2015.

| | Amount of active ingredient in kg (percent) | DDDch ^a (percent) | DDDvet ^b (percent) | Ratio | DCDch ^c (percent) | DCDvet ^d (percent) | Ratio | treatment duration ch | treatment duration vet | ratio |
|-----------------------------|---|------------------------------|-------------------------------|--------|------------------------------|-------------------------------|--------|-----------------------|------------------------|--------|
| Overall Result | 421 | 1,805,494 | 1,456,771 | -19.3% | 433,678 | 303,913 | -29.9% | 3.7 | 4.0 | 8.1% |
| AGE GROUP | | | | | | | | | | |
| Piglets | 15 (3.6%) | 473,922 (26.3%) | 428,546 (29.4%) | -9.6% | 230,237 (53.1%) | 132,433 (43.6%) | -42.5% | 2.9 | 3.5 | 20.7% |
| Weaners | 208 (49.4%) | 1,143,175 (63.3%) | 878,525 (60.3%) | -23.2% | 151,483 (34.9%) | 136,136 (44.8%) | -10.1% | 5.6 | 5.0 | -10.7% |
| Finisher pigs | 138 (32.8%) | 159,719 (8.8%) | 122,493 (8.4%) | -23.3% | 40,894 (9.4%) | 27,566 (9.1%) | -32.6% | 3.7 | 4.0 | 8.1% |
| Sows | 60 (14.2%) | 28,678 (1.6%) | 27,207 (1.9%) | -5.1% | 11,064 (2.5%) | 7,778 (2.6%) | -29.7% | 2.9 | 3.6 | 24.1% |
| ADMINISTRATION ROUTE | | | | | | | | | | |
| Oral | 0.1 (0.0%) | 13,856 (0.7%) | 10,080 (0.7%) | -27.2% | 4,435 (1.0%) | 2,432 (0.8%) | -45.2% | 3.3 | 4.2 | 27.3% |
| Injection | 114 (27.1%) | 620,458 (34.4%) | 579,947 (39.8%) | -6.5% | 309,277 (71.3%) | 182,839 (60.2%) | -40.9% | 2.7 | 3.4 | 25.9% |
| Premix | 307 (72.9%) | 1,171,180 (64.9%) | 866,744 (59.5%) | -26.0% | 119,966 (27.7%) | 118,642 (39.0%) | -1.1% | 9.9 | 7.6 | -23.2% |

AMU is measured as active ingredient and by Swiss and European defined dosage grouped by age category and administration route. The ratio between the number of treatment days and treatments, as well as the overall observed mean treatment durations based on Swiss doses or the doses of the European Medicine Agency (EMA) was calculated. Numbers in bold shown a ratio > ±20%.

^aDDDch: Number of treatment days based on Swiss Defined Daily Doses.
^bDDDvet: Number of treatment days based on Defined Daily Doses of the European Medicine Agency (EMA).
^cDCDch: Number of treatments based on Swiss Defined Course Doses.
^dDCDvet: Number of treatments based on Defined Course Doses of the European Medicine Agency (EMA).

Swiss Veterinary Medicines Compendium (23). The detailed procedure of defining the national doses and all values for DDDch and DCDch is accessible as **Supplementary Data**. A product and the farm using it were excluded from the study when corresponding DDD/DCDvet values had not been published by the EMA either for the specific antimicrobial ingredient or a comparable antimicrobial ingredient, a given combination of substances or a specific administration route.

The number of defined doses and the amount of prescribed antimicrobial ingredient were calculated in total, for the different age groups, different administration routes (injection, oral, and premix) and for all antimicrobial classes. The term premix included all antimicrobial ingredients to be administered via the feed and/or water. By dividing the results using DDD/DCDvet by those based on DDD/DCDch, differences of Swiss or European definitions were investigated for the calculated AMU. The results of this calculations were termed ratio. A positive ratio with results > 0 indicated a higher number of estimated treatment days or treatments could be observed when using the European definitions DDD vet or DCDvet. In addition, the overall observed mean treatment durations given by the Swiss or European defined values were compared in the same way.

For the evaluation of the AMU at the farm level and in order to compare the consumption on different farms, the number of kept (sows) or produced pigs (other age groups) in the year 2015 were taken into account. The amount of prescribed antimicrobial ingredients was divided by the different defined doses, the standard weights and the number of pigs for each age group. If necessary, the results of the different age groups were summarized together and the number of Defined Doses per farm

TABLE 2 | Total antimicrobial use (AMU) measured as active ingredient and by Swiss and European defined dosage grouped by different antimicrobial classes.

| Antimicrobial classes | Amount of active ingredient in kg | DDDch ^a | DDDvet ^b | DCDch ^c | DCDvet ^d |
|-----------------------|-----------------------------------|--------------------|---------------------|--------------------|---------------------|
| Aminoglycosides | 25.7 | 67,273 | 59,973 | 20,918 | 15,255 |
| Amphenicols | 0.03 | 44 | 69 | 22 | 22 |
| Cephalosporins | 0.3 | 2,200 | 2,299 | 733 | 636 |
| Fluoroquinolones | 6.0 | 171,518 | 127,880 | 57,173 | 39,064 |
| Lincosamides | 0.7 | 26,217 | 20,456 | 2,777 | 2,997 |
| Macrolides | 21.4 | 293,108 | 120,006 | 33,286 | 15,148 |
| Penicillins | 77.8 | 385,507 | 388,221 | 229,006 | 120,394 |
| Pleuromutilins | 4.0 | 14,388 | 11,289 | 1,188 | 1,623 |
| Polypeptides | 26.0 | 335,498 | 402,708 | 33,687 | 43,006 |
| Pyrimidines | 2.1 | 6,613 | 6,252 | 1,653 | 1,705 |
| Sulfonamides | 144.1 | 228,817 | 98,192 | 23,946 | 30,848 |
| Tetracyclins | 113.1 | 274,311 | 219,426 | 29,289 | 33,215 |

^aDDDch: Number of treatment days based on Swiss Defined Daily Doses.

^bDDDvet: Number of treatment days based on Defined Daily Doses of the European Medicine Agency (EMA).

^cDCDch: Number of treatments based on Swiss Defined Course Doses.

^dDCDvet: Number of treatments based on Defined Course Doses of the European Medicine Agency (EMA).

was calculated.

$$\text{Number of Defined Doses per farm} = \frac{\text{total amount of prescribed antimicrobial ingredient per farm and age group (mg)}}{\text{DDDvet or DDDch or DCDvet or DCDch} \left(\frac{\text{mg}}{\text{kg}} \right) \times \text{standard weight of age group (kg)} \times \text{number of pigs per farm and age group}}$$

Data Processing and Statistical Analysis

The preparation of all operating farm data and the calculation of the number of defined doses was carried out using Microsoft Excel 2011 (Microsoft, Redmond, WA, USA). The statistical analysis and preparation of graphs to visualize the results was performed with R (<https://cran.r-project.org>). Differences between the tested groups having a $P \leq 0.05$ were considered statistically significant. The data for calculated AMU on farm level was tested for normality by the Shapiro-Wilk test. The association of Swiss and European dosages for a possible AMU monitoring system on the farms was evaluated using scatterplots and correlation analysis performed by Spearman's rho test. The differences between the various farm structures were investigated using the Kruskal-Wallis test for independent samples and *post hoc* pairwise analysis (Bonferroni correction).

RESULTS

AMU Quantification per Age Group and Administration Route

In this study, the AMU was calculated at 1,805,494 DDDch and 433,678 DCDch when based on Swiss values, compared to 1,456,771 DDDvet (−19.3% ratio) and 303,913 DCDvet (−29.9% ratio) based on European defined doses (**Table 1**). The mean treatment duration was 3.7 days based on Swiss values and 4.0 days based on European values. The largest fraction of DDD was calculated for weaners, regardless of Swiss DDDch (64.4%) or European DDDvet (60.3%), whereas for DCDs based on Swiss definitions, piglets represented the major part of the treatments (53.1%). Based on European definitions most calculated course doses were observed for weaners (44.8%). Ratios of more than 20% between the calculated numbers of DDD/DCDch and

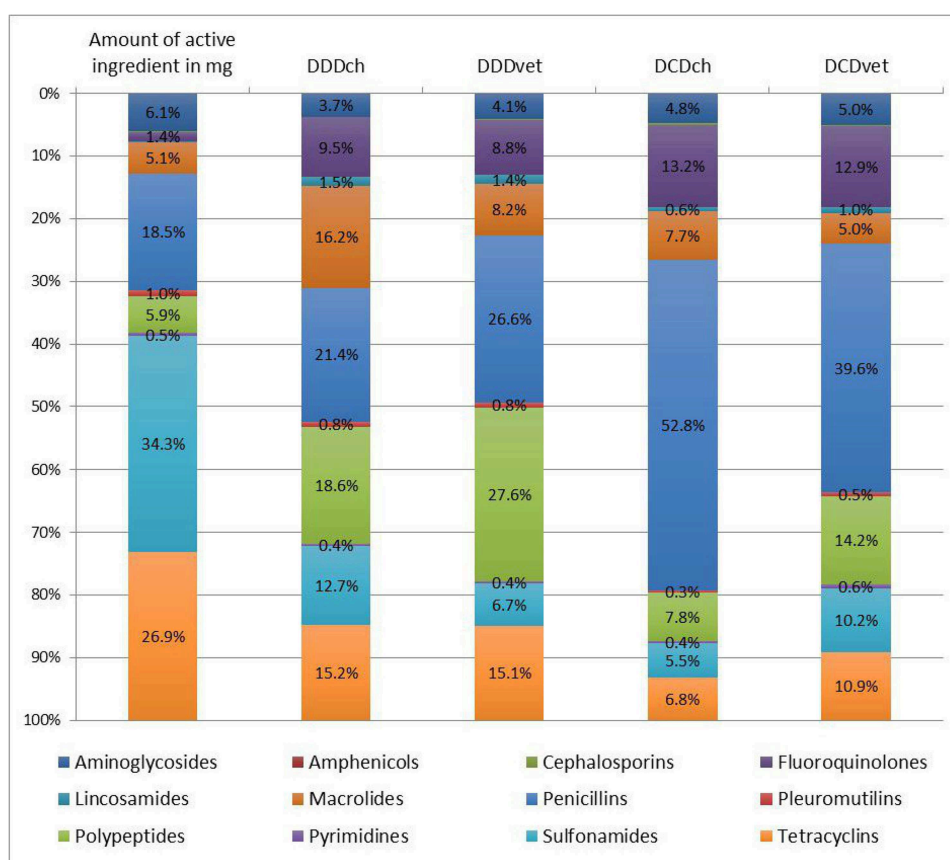


FIGURE 1 | Relative distribution of antimicrobial use (AMU) between different antimicrobial classes measured either as the amount of active ingredient or as the number of defined daily doses (DDD) or defined course doses (DCD), respectively. DDD and DCD were calculated with Swiss values (DDDch and DCDch) or European values (DDDvet or DCDvet) published by the European Medicine Agency (EMA). (Amphenicols and cephalosporins as well as lincosamides are not inscribed due to the low values).

DDD/DCDvet, respectively could be observed for the number of DDDch/vet of weaners and finisher pigs and for DCDch/vet of piglets, finisher pigs, and sows. The largest quantity of active ingredients was given to the groups of weaners (49.4%), followed by finisher pigs (32.7%), sows (14.2%), and piglets (3.6%). When investigating the different administration routes by the number of defined doses, premixes represented the largest proportion calculated by DDDch/vet (64.9/59.5%) in contrast to injectable products when calculating the number of DCDch/vet (71.3/60.2%). Relative differences of more than $\pm 20\%$ could be observed for oral and premix treatments when calculated in DDDch and DDDvet, respectively, and for oral and parenteral treatments when calculated in DCDch or DCDvet. The treatment duration was longer when the calculation was based on DDD/DCDvet compared to DDD/DCDch, except for treatments of weaners in general and for treatments with premixes.

AMU Quantification per Antimicrobial Classes

The amount of active ingredient and the calculated numbers of defined doses for different antimicrobial classes were summarized in **Table 2** and the relative distribution was visualized in **Figure 1**. Considering the amount of active ingredient used, the classes of sulfonamides (144,086,000 mg/34.3%), tetracyclines (113,122,600 mg/26.9%), and penicillins (77,788,850 mg/18.5%) represented the largest proportion of the total usage, whereas when using defined daily doses, penicillins (DDDch: 385,507/21.4%; DDDvet: 388,221/26.6%) and polypeptides (DDDch: 335,498/18.6%; DDDvet: 402,708/27.6%) were the most frequent. Macrolides were observed to represent 16.2% of the total usage (293,108 treatment days) calculated in DDDch. Penicillins (DCDch: 229,006/52.8%; DCDvet: 120,394/39.6%) and fluoroquinolones (DCDch: 57,173/13.2%; DCDvet: 39,064/12.9%) were common for the number of total treatments, as well as polypeptides (DCDvet: 43,006/14.2%) for calculations based on the European values. The percentage of fluoroquinolones in total AMU was 1.4% when considering the amount in mg, compared to 8.8 and 13.2% when calculating DDDvet and DCDch, respectively.

A more detailed, combined consideration of age groups, administration routes, and antimicrobial class data shows that injection was the most frequent administration route for piglets independent of the method used for calculation, and that within this group penicillins and fluoroquinolones were the most frequently used antimicrobials (**Table 3**). The use of premixes was the most frequently used administration route for weaners independent of the indicator used and polypeptides were most frequently used when considering the number of defined daily doses. For the number of calculated doses based on DDD/DCDch, frequent use of macrolides was notable in the premixes given to weaners whereas sulfonamides and tetracyclines were more frequently used when the calculation was based on DDD/DCDvet. In terms of the finisher pig group, injection and premixes were observed with similar frequencies for administration routes, when either daily doses or course doses were the basis of the calculation. Oral administration of

premixes was the most common administration route when calculating AMU based on defined doses. Contrastingly, when calculating in course doses, injections represented the largest proportion of treatments. Penicillins and aminoglycosides were frequently used injections for finisher pigs and tetracyclines were the most commonly used antimicrobial class given as premix. As was the case in weaners, macrolides represented a considerable proportion of treatments based on DDDch as well as DCDch. In sows, most antimicrobials were given by injections and within this group, most of the antimicrobials administered belonged to the antimicrobial classes of penicillins and fluoroquinolones. The most frequently administered antimicrobial class provided as a premix was the class of penicillins. An administration of oral antimicrobials without feed or water was only observed for fluoroquinolones and polypeptides in piglets and on only two farms with a small amount in weaners.

AMU Monitoring on Farm Level

Each dataset was tested for normality by Shapiro-Wilk test and for all datasets, independent of Swiss or European measuring method or type of farm, the null hypothesis was rejected (each $P < 0.001$).

The scatterplot of calculated defined daily doses (DDD) and defined course doses (DCD), analyzing the association between Swiss (ch) and European (vet) definitions, is given in **Figure 2**. As shown, both the calculated number of daily doses and the calculated number of course doses showed a positive correlation between results on the farm level by Spearman's rho test.

Consideration of structure of the various farms pointed to a higher amount of calculated AMU per farm and per year on farrow-to-finisher farms and piglet-producing farms compared to finisher farms for all Swiss or European values of defined doses ($P < 0.001$) by Kruskal-Wallis-test and subsequent *post hoc* pairwise analysis (**Table 4**, **Figure 3**). In terms of calculated DDDch-numbers the median values were 4.40, 4.88, and 0.27 for farrow-to-finisher, piglet-producing and finisher farms, respectively. No significant difference between the farrow-to-finisher farms and the piglet-producers was observed for any of the used values.

DISCUSSION

This study shows that although evaluating AMU for the pig sector at the farm level based either on Swiss or European defined doses leads to similar results with a positive correlated association, there were still deviations in detail, i.e., in the assessment of the different active substance classes, different administration routes and various age groups. A possible on farm AMU monitoring system will arrive at similar conclusions and farms with low or high AMU consumption will be similarly assessed using both methods. Since the Swiss definitions are based on individual national approvals in comparison to the average EMA definitions collected from nine countries, the Swiss definitions seem more robust for a national evaluation of active substance classes, administration routes and age groups.

The challenge of collecting adequate information on AMU in the field is well-known and described in the literature (15). Since

TABLE 3 | Distribution of antimicrobial use (AMU) per different age categories, administration routes and antimicrobial classes measured as active ingredient and by Swiss and European defined dosage.

| Age group | Administration route | Antimicrobial classes | Amount of active ingredient in mg | | DDDch ^a (n) (%) | | DDDvet ^b (n) (%) | | DCDch ^c (n) (%) | | DDDvet ^d (n) (%) | |
|-----------|----------------------|-----------------------|-----------------------------------|--------------|----------------------------|--------------|-----------------------------|--------------|----------------------------|--------------|-----------------------------|--------------|
| Piglets | Oral | | 15,117,075 | | 473,922 | | 428,546 | | 230,237 | | 132,433 | |
| | | | 118,250 | 0.8% | 13,833 | 2.9% | 10,065 | 2.3% | 4,428 | 1.9% | 2,428 | 1.8% |
| | | Fluoroquinolones | 83,050 | 70.2% | 12,458 | 90.1% | 8,305 | 82.5% | 4,153 | 93.8% | 2,076 | 85.5% |
| | Injection | Polypeptides | 35,200 | 29.8% | 1,375 | 9.9% | 1,760 | 17.5% | 275 | 6.2% | 352 | 14.5% |
| | | | 14,764,825 | 97.7% | 450,340 | 95.0% | 406,781 | 94.9% | 224,835 | 97.7% | 128,760 | 97.2% |
| | | Aminoglycosides | 2,662,850 | 18.0% | 39,802 | 8.8% | 36,445 | 9.0% | 13,419 | 6.0% | 9,661 | 7.5% |
| | | Cephalosporins | 7,875 | 0.1% | 880 | 0.2% | 916 | 0.2% | 293 | 0.1% | 259 | 0.2% |
| | | Fluoroquinolones | 1,281,725 | 8.7% | 129,323 | 28.7% | 95,830 | 23.6% | 43,108 | 19.2% | 29,632 | 23.0% |
| | | Lincosamides | 297,500 | 2.0% | 14,875 | 3.3% | 9,535 | 2.3% | 2,125 | 0.9% | 2,010 | 1.6% |
| | | Macrolides | 98,000 | 0.7% | 2,450 | 0.5% | 1,885 | 0.5% | 817 | 0.4% | 471 | 0.4% |
| | | Penicillins | 10,118,275 | 68.5% | 257,065 | 57.1% | 253,251 | 62.3% | 163,096 | 72.5% | 83,993 | 65.2% |
| | | Pleuromutilins | 20,000 | 0.1% | 400 | 0.1% | 417 | 0.1% | 133 | 0.1% | 227 | 0.2% |
| | | Pyrimidines | 22,000 | 0.1% | 1,857 | 0.4% | 1,833 | 0.5% | 464 | 0.2% | 500 | 0.4% |
| | | Sulfonamides | 110,000 | 0.7% | 1,857 | 0.4% | 1,782 | 0.4% | 464 | 0.2% | 480 | 0.4% |
| | | Tetracyclins | 146,600 | 1.0% | 1,833 | 0.4% | 4,887 | 1.2% | 916 | 0.4% | 1,527 | 1.2% |
| | Premix | | 234,000 | 1.5% | 9,750 | 2.1% | 11,700 | 2.7% | 975 | 0.4% | 1,245 | 0.9% |
| | | Polypeptides | 234,000 | 100.0% | 9,750 | 100.0% | 11,700 | 100.0% | 975 | 100.0% | 1,245 | 100.0% |
| Weaners | Oral | | 207,658,150 | | 1,143,175 | | 878,525 | | 151,483 | | 136,136 | |
| | | | 450 | 0.0% | 23 | 0.0% | 15 | 0.0% | 8 | 0.0% | 4 | 0.0% |
| | Injection | Fluoroquinolones | 450 | 100.0% | 23 | 100.0% | 15 | 100.0% | 8 | 100.0% | 4 | 100.0% |
| | | | 8,654,000 | 4.2% | 82,799 | 7.2% | 89,073 | 10.1% | 42,440 | 28.0% | 28,684 | 21.1% |
| | | Aminoglycosides | 755,300 | 8.7% | 5,946 | 7.2% | 4,621 | 5.2% | 1,790 | 4.2% | 1,252 | 4.4% |
| | | Cephalosporins | 12,500 | 0.1% | 486 | 0.6% | 508 | 0.6% | 162 | 0.4% | 141 | 0.5% |
| | | Fluoroquinolones | 567,400 | 6.6% | 21,078 | 25.5% | 16,860 | 18.9% | 7,026 | 16.6% | 5,237 | 18.3% |
| | | Lincosamides | 62,500 | 0.7% | 1,042 | 1.3% | 668 | 0.7% | 149 | 0.4% | 141 | 0.5% |
| | | Macrolides | 100,000 | 1.2% | 833 | 1.0% | 641 | 0.7% | 278 | 0.7% | 160 | 0.6% |
| | | Penicillins | 5,955,400 | 68.8% | 46,766 | 56.5% | 52,806 | 59.3% | 30,355 | 71.5% | 17,753 | 61.9% |
| | | Pleuromutilins | 10,000 | 0.1% | 67 | 0.1% | 69 | 0.1% | 22 | 0.1% | 38 | 0.1% |
| | | Pyrimidines | 36,400 | 0.4% | 1,264 | 1.5% | 1,011 | 1.1% | 316 | 0.7% | 276 | 1.0% |
| | | Sulfonamides | 182,000 | 2.1% | 1,264 | 1.5% | 1,083 | 1.2% | 316 | 0.7% | 310 | 1.1% |
| | | Tetracyclins | 972,500 | 11.2% | 4,052 | 4.9% | 10,806 | 12.1% | 2,026 | 4.8% | 3,377 | 11.8% |
| | Premix | | 199,003,700 | 95.8% | 1,060,353 | 92.8% | 789,437 | 89.9% | 109,036 | 72.0% | 107,448 | 78.9% |
| | | Aminoglycosides | 268,400 | 0.1% | 10,167 | 1.0% | 6,578 | 0.8% | 484 | 0.4% | 828 | 0.8% |
| | | Lincosamides | 268,400 | 0.1% | 10,167 | 1.0% | 10,167 | 1.3% | 484 | 0.4% | 828 | 0.8% |
| | | Macrolides | 15,594,000 | 7.8% | 264,722 | 25.0% | 108,292 | 13.7% | 29,222 | 26.8% | 13,260 | 12.3% |
| | | Penicillins | 5,613,500 | 2.8% | 22,598 | 2.1% | 27,517 | 3.5% | 4,520 | 4.1% | 2,613 | 2.4% |
| | | Pleuromutilins | 400,000 | 0.2% | 4,444 | 0.4% | 3,436 | 0.4% | 317 | 0.3% | 412 | 0.4% |

(Continued)

TABLE 3 | Continued

| Age group | Administration route | Antimicrobial classes | Amount of active ingredient in mg | | DDDch ^a (n) (%) | | DDDvet ^b (n) (%) | | DCDch ^c (n) (%) | | DDDvet ^d (n) (%) | |
|---------------|----------------------|-----------------------|-----------------------------------|--------------|----------------------------|--------------|-----------------------------|--------------|----------------------------|--------------|-----------------------------|--------------|
| Finisher pigs | Injection | Polypeptides | 22,934,400 | 11.5% | 318,533 | 30.0% | 382,240 | 48.4% | 31,853 | 29.2% | 40,664 | 37.8% |
| | | Sulfonamides | 91,210,000 | 45.8% | 200,556 | 18.9% | 82,618 | 10.5% | 20,056 | 18.4% | 26,120 | 24.3% |
| | | Tetracyclins | 62,715,000 | 31.5% | 229,167 | 21.6% | 168,589 | 21.4% | 22,099 | 20.3% | 22,723 | 21.1% |
| | | | 137,539,345 | | 159,719 | | 122,493 | | 40,894 | | 27,566 | |
| | | | 36,317,845 | 26.4% | 59,832 | 37.5% | 58,296 | 47.6% | 31,176 | 76.2% | 17,751 | 64.4% |
| | | Aminoglycosides | 9,080,625 | 25.0% | 8,386 | 14.0% | 9,221 | 15.8% | 3,872 | 12.4% | 2,627 | 14.8% |
| | | Amphenicols | 32,700 | 0.1% | 44 | 0.1% | 69 | 0.1% | 22 | 0.1% | 22 | 0.1% |
| | | Cephalosporins | 31,500 | 0.1% | 315 | 0.5% | 332 | 0.6% | 105 | 0.3% | 89 | 0.5% |
| | | Fluoroquinolones | 108,125 | 0.3% | 915 | 1.5% | 713 | 1.2% | 305 | 1.0% | 220 | 1.2% |
| | | Lincosamides | 30,000 | 0.1% | 120 | 0.2% | 77 | 0.1% | 17 | 0.1% | 16 | 0.1% |
| | Premix | Macrolides | 653,600 | 1.8% | 1,307 | 2.2% | 1,006 | 1.7% | 436 | 1.4% | 251 | 1.4% |
| | | Penicillins | 24,298,495 | 66.9% | 46,202 | 77.2% | 41,541 | 71.3% | 25,360 | 81.3% | 12,839 | 72.3% |
| | | Pleuromutilins | 90,000 | 0.2% | 144 | 0.2% | 150 | 0.3% | 48 | 0.2% | 82 | 0.5% |
| | | Pyrimidines | 58,000 | 0.2% | 377 | 0.6% | 387 | 0.7% | 94 | 0.3% | 105 | 0.6% |
| | | Sulfonamides | 290,000 | 0.8% | 377 | 0.6% | 414 | 0.7% | 94 | 0.3% | 129 | 0.7% |
| | | Tetracyclins | 1,644,800 | 4.5% | 1,645 | 2.7% | 4,386 | 7.5% | 822 | 2.6% | 1,371 | 7.7% |
| | | | 101,221,500 | 73.6% | 99,887 | 62.5% | 64,197 | 52.4% | 9,718 | 23.8% | 9,815 | 35.6% |
| | | Macrolides | 4,897,000 | 4.8% | 23,767 | 23.8% | 8,162 | 12.7% | 2,525 | 26.0% | 999 | 10.2% |
| | | Penicillins | 1,950,000 | 1.9% | 1,917 | 1.9% | 2,294 | 3.6% | 383 | 3.9% | 218 | 2.2% |
| | | Pleuromutilins | 350,000 | 3.5% | 9,333 | 9.3% | 7,216 | 11.2% | 667 | 6.9% | 864 | 8.8% |
| Sows | Injection | Polypeptides | 1,752,000 | 1.7% | 5,840 | 5.8% | 7,008 | 10.9% | 584 | 6.0% | 746 | 7.6% |
| | | Sulfonamides | 42,145,000 | 41.6% | 21,567 | 21.6% | 9,162 | 14.3% | 2,210 | 22.7% | 2,897 | 29.5% |
| | | Tetracyclins | 46,977,500 | 46.4% | 37,464 | 37.5% | 30,355 | 47.3% | 3,349 | 34.5% | 4,091 | 41.7% |
| | | | 59,835,480 | | 28,678 | | 27,207 | | 11,064 | | 7,778 | |
| | | | 54,560,980 | 91.2% | 27,489 | 95.9% | 25,797 | 94.8% | 10,826 | 97.8% | 7,644 | 98.3% |
| | | Aminoglycosides | 12,929,300 | 23.7% | 2,972 | 10.8% | 3,108 | 12.0% | 1,352 | 12.5% | 885 | 11.6% |
| | | Cephalosporins | 236,525 | 0.4% | 519 | 1.9% | 544 | 2.1% | 173 | 1.6% | 148 | 1.9% |
| | | Fluoroquinolones | 3,930,475 | 7.2% | 7,722 | 28.1% | 6,157 | 23.9% | 2,574 | 23.8% | 1,895 | 24.8% |
| | | Lincosamides | 15,000 | 0.0% | 14 | 0.0% | 9 | 0.0% | 2 | 0.0% | 2 | 0.0% |
| | | Macrolides | 62,000 | 0.1% | 28 | 0.1% | 22 | 0.1% | 9 | 0.1% | 5 | 0.1% |
| | Premix | Penicillins | 24,578,680 | 45.0% | 9,769 | 35.5% | 9,401 | 36.4% | 5,054 | 46.7% | 2,844 | 37.2% |
| | | Pyrimidines | 1,993,800 | 3.7% | 3,116 | 11.3% | 3,021 | 11.7% | 779 | 7.2% | 824 | 10.8% |
| | | Sulfonamides | 10,149,000 | 18.6% | 3,197 | 11.6% | 3,133 | 12.1% | 806 | 7.4% | 914 | 12.0% |
| | | Tetracyclins | 666,200 | 1.2% | 151 | 0.6% | 404 | 1.6% | 76 | 0.7% | 126 | 1.7% |
| | | | 5,274,500 | 8.8% | 1,189 | 4.1% | 1,410 | 5.2% | 238 | 2.2% | 134 | 1.7% |
| | | Penicillins | 5,274,500 | 100.0% | 1,189 | 100.0% | 1,410 | 100.0% | 238 | 100.0% | 134 | 100.0% |

Numbers in bold are mentioned in the results part of the study.

^aDDDch: Number of treatment days based on Swiss Defined Daily Doses.

^bDDDvet: Number of treatment days based on Defined Daily Doses of the European Medicine Agency (EMA).

^cDCDch: Number of treatments based on Swiss Defined Course Doses.

^dDCDvet: Number of treatments based on Defined Course Doses of the European Medicine Agency (EMA).

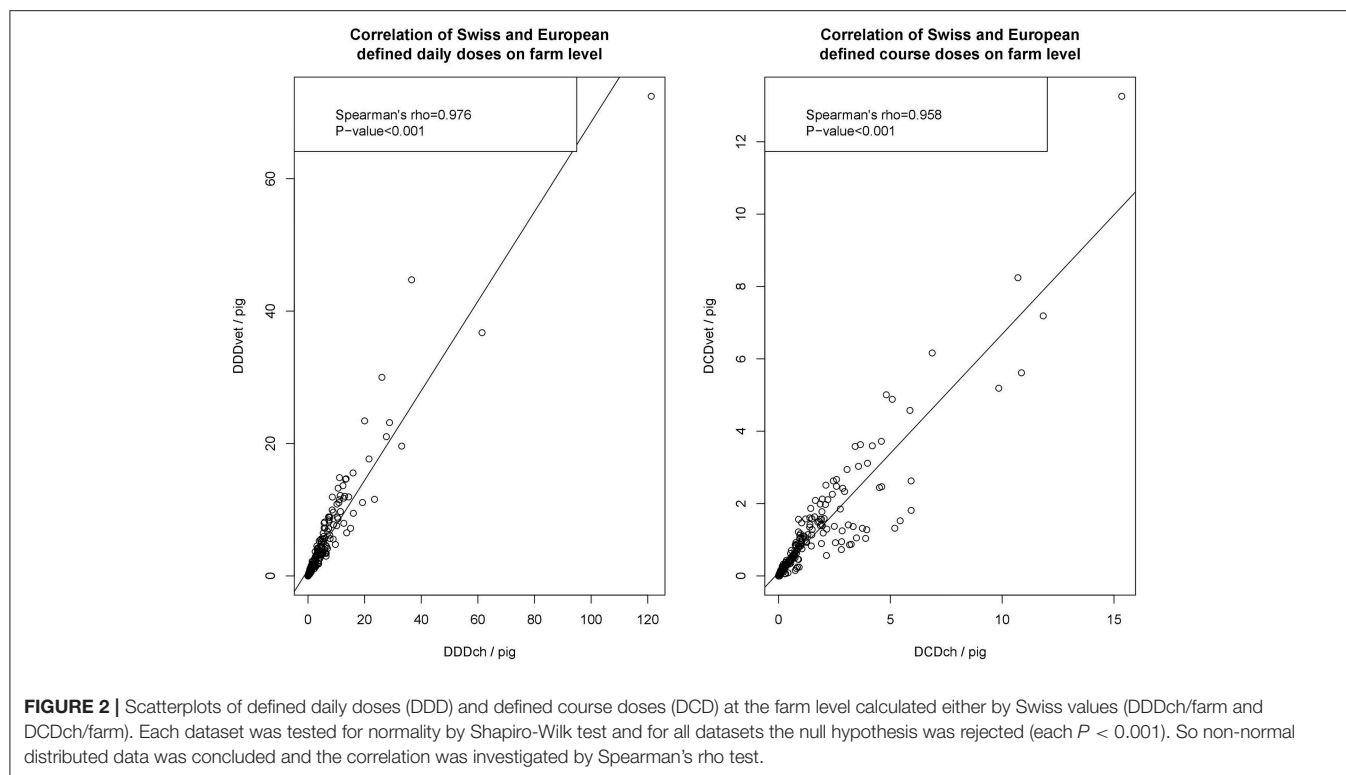


TABLE 4 | Median values of the defined daily doses (DDD) and defined course doses (DCD) based on the number of Switzerland (DDDch/farm and DCDch/farm) and the European Medicine Agency (DDDvet/farm and DCDvet/farm) for the different type of farms (farrow-to-finish farm, finishing farm and piglet-producing farm).

| | DDDch/farm | DDDvet/farm | DCDch/farm | DCDvet/farm |
|--------------------------|-------------------|-------------------|------------------|-------------------|
| 1) Farrow-to-finish farm | 4.40 (0.67–16.02) | 3.63 (0.83–15.46) | 1.43 (0.27–4.48) | 0.98 (0.239–3.63) |
| 2) Finishing farm | 0.27* (0–3.82) | 0.26* (0–2.75) | 0.08* (0–0.70) | 0.077* (0–0.50) |
| 3) Piglet-producing farm | 4.88 (0.96–12.45) | 3.99 (1.04–12.04) | 1.22 (0.29–4.61) | 1.05 (0.26–2.65) |

10 and 90% percentiles are given in brackets. Each dataset was tested for normality by Shapiro-Wilk tests and for all datasets the null hypothesis was rejected (each $P < 0.001$). So non-normal distributed data was concluded. By performing Kruskal-Wallis test for independent samples and post hoc pairwise analysis (Bonferroni correction) significant differences between finishing farm and farrow-to-finish-farm respectively, piglet-producing farm could be observed (each $P < 0.001$). No significant differences between farrow-to-finish farm and piglet-producing farm could be observed (each $P > 0.05$). * $P < 0.001$ (to 1 and 3).

the participation in the present study and supply of data was voluntary, some bias cannot be completely ruled out due to the fact that knowledge and motivation of farmers have an influence on AMU (24). We consider the coverage of the study population to be adequate for our study goals with 3.3% of all Swiss pig farms and 9.5% of all sows, and it allows to deduce that especially larger farms seemed to be more motivated to participate in the study.

Since the data underlying this study did not include a record about the length of pigs' stay in the farrowing unit, the nursery unit and the fattening unit, it is not feasible to make an exact evaluation of how many theoretical treatment days or treatments would be possible in the life span of a pig, as calculated by Timmermann et al. (25). However, the calculation behind the number of dosages on farm level is based on the population of animals present or produced during 1 year and this makes it comparable to other systems using defined doses to estimate AMU per farm in livestock (11–13).

Since the present study is based on calculations from prescribed amounts, the exact amounts of antimicrobials used by the farmer cannot be assessed and overdosing as well as underdosing could bias the results and the study only allows a statistical estimation of the probable AMU.

Another aspect of this study which is shown in **Table 1** is the different evaluation of monitoring systems based either on the measurement of the amount of active ingredient or on the measurement of application equivalents such as defined doses: due to the lower standard weight of piglets, a considerable number of defined treatments can be performed with an amount of antimicrobial suitable for a single treatment of just one sow. As a consequence, the observed amount of active ingredients for e.g., piglets was low whereas the number of calculated doses was high. This is in line with prior studies (26) and EMA advice cautioning that differences in dosing between species and substances must be taken into account when using DDD and DCD values (19).

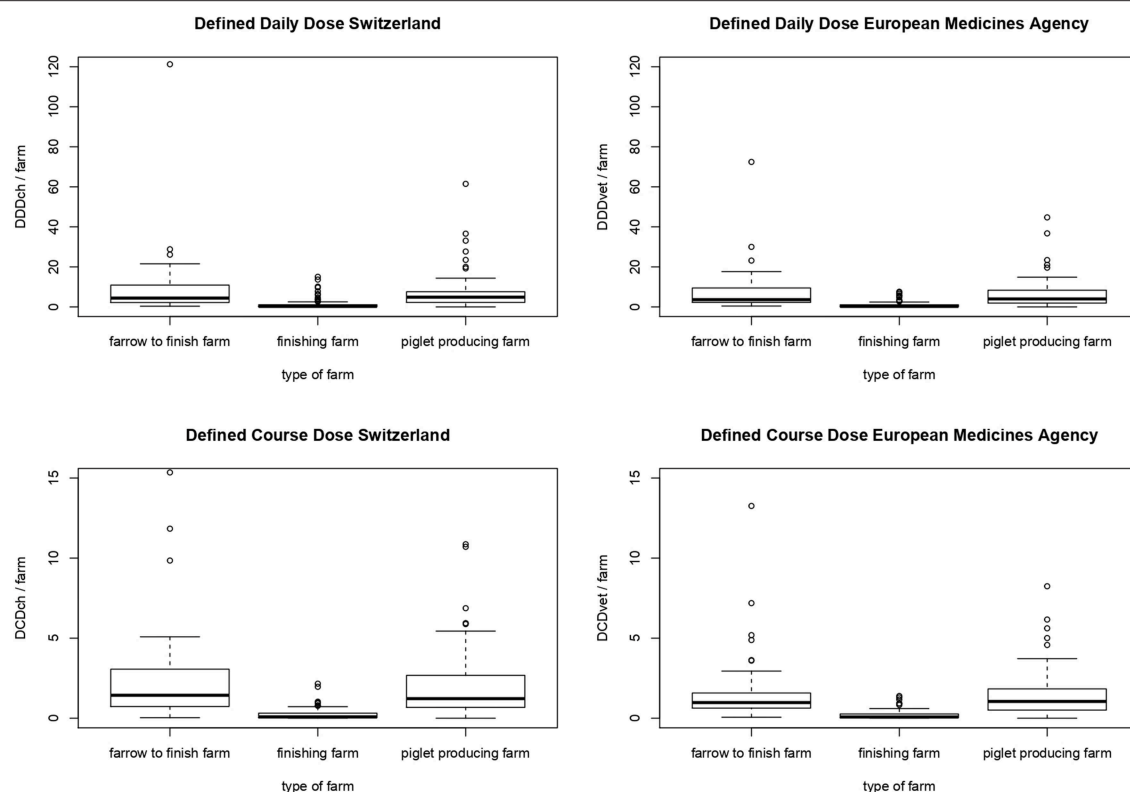


FIGURE 3 | Comparison of antimicrobial use in different types of farms (farrow-to-finish farms, finishing farms and piglet-producing farms) measured by the number of defined daily doses (DDD) and defined course doses (DCD) per farm based on the values of Switzerland (DDDch/farm and DCDch/farm) and the European Medicine Agency (DDDvet/farm and DCDvet/farm). Each dataset was tested for normality by Shapiro-Wilk test and for all datasets the null hypothesis was rejected (each $P < 0.001$). So non-normal distributed data was concluded. By performing Kruskal-Wallis test for independent samples and *post hoc* pairwise analysis (Bonferroni correction) significant differences between finishing farm and farrow-to-finish-farm respectively, piglet-producing farm could be observed (each $P < 0.001$). No significant differences between farrow-to-finish farm and piglet-producing farm could be observed (each $P > 0.05$).

In general, a low value for a defined dose results in a higher number of calculated or estimated doses in a population (17). This explains some differences between the number of DDDch or DCDch on the one side and DDDvet and DCDvet on the other side. For example, macrolides showed a difference in calculated use depending on whether Swiss or European definitions were chosen. As a previous study showed, there are six Swiss premix products containing the macrolide tylosin with much lower defined daily and course doses compared to the values of the EMA (20), thus explaining the relatively high number of DDDch and DCDch in this category. This general understanding can also be used to explain the results in Table 1. All groups with a high ratio between the calculation based on Swiss or European definitions come by a frequent use with approvals whose DDDch and DCDch values differ strongly from the DDDvet and DCDvet values.

In accordance with a recently published study, the animal groups with the highest numbers of treatment days and total number of treatments observed were weaners (DDDch, DDDvet, and DCDvet) and piglets (DCDch) (27). These groups are most susceptible to bacterial infections and, at least for the weaners, frequent group therapies at weaning can be assumed,

which is reflected in the high proportion of treatments with premixes, as described by other studies (28). This assumption is also underlined by the fact, that a longer Swiss treatment duration could be observed only for weaned piglets and for premixes and a relationship between both findings could be hypothesized. Thus, young age groups should already be considered in terms of resistance prevention and the use of group therapies by premixes in feed in these groups should be critically re-evaluated (29).

Furthermore, when calculating the number of DDDs, relatively high use could be observed for premixes and in contrast, a relatively high total number of course doses could be observed for injections in this study. This can be explained by the comparison of treatment durations between injections and premixes, since the number of calculated course doses decreases with the increase in treatment duration of the premixes. Previous publications confirmed the high proportion of premixes used in the pig sector in Switzerland (30, 31). An increased risk of development of resistance for specific active substances and bacteria is documented by this administration route (32). Thus, group therapies should be reduced to the necessary minimum.

A relatively high proportion of treatments with Highest Priority Critically Important Antimicrobials (HPCIAAs) could be observed in this study (e.g., 44.8% of DDDvet's). These findings are comparable to results recently published from the EFFORT consortium (27), but varying from results of a previous study, where a lower AMU quantification of HPCIAAs for pigs in Switzerland based on total amount of given active ingredient was observed (33). Due to the documented spread of resistance genes e.g., against fluoroquinolones in the pig sector (34), every use of these substances should be of concern and further research investigating restriction of indications and potential reductions in usage is needed.

The results from the different farm types show again that the younger age groups are most frequently treated. Both, farrow-to-finishing farm as well as piglet-producing farms in contrast to the finishing farms keep the high consumption age groups of piglets and weaners. This could explain the significant difference. Due to the small number of calculated defined doses of finisher pigs, no significant difference between farrow-to-finishing and piglet-producing farms was observed.

In order to gain a better understanding of the differences between these individual farms, further studies are needed to examine the role of the farmer (23) as well as AMU quantification and performance data (35).

CONCLUSION

In summary, this study demonstrated a general association of the AMU systems at the farm level, nevertheless, differences were seen in detail according to whether the calculation was based on individual Swiss or average European values. The benefit of the European values for internationally comparative AMU monitoring is undisputed, but for a detailed evaluation, Swiss definitions could be more accurate as they are based on the specific approvals of the country. This must be considered in order to understand international AMU comparisons in the future. The study also highlighted the need to further evaluation for the use of HPCIAAs.

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DATA AVAILABILITY

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

Since this was only data that had no influence on the actual treatment of the animals, an animal welfare permit was not required. No manipulations or something similar were carried out on any animals.

AUTHOR CONTRIBUTIONS

DK, XS, CM, and TE contributed conception and design of the study. TE organized the database and performed the statistical analysis. CM is responsible for the correctness of the pharmacological formulations and the part in the manuscript about measurement methodologies. TE wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fvets.2019.00240/full#supplementary-material>

- sales-veterinary-antimicrobial-agents-30-european-countries-2015_en.pdf (accessed February 04, 2019).
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